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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/064,000	ELIA, JAMES P.	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007 and 25 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *382-406* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *382-406* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 04/30/2007 and 05/25/2007 have been entered.

2. Claims 382-406 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647. The Examiner for this Application is now Daniel C. Gamett.

5. Upon review of the record, it is apparent to this Examiner that Applicant believes that the rejections of record are rooted in an inability of the examiner to understand the terminology of the art. Applicant stated this plainly on page 26 of the remarks filed 04/30/2007, "Applicant believes that once the Examiner's misunderstanding of the questioned terminology is transformed into an understanding consistent with that used by a skilled person in the medical art, there should be no further issue remaining." Another example is found on page 13, "...the lack of understanding of the disputed medical terminology appears to be that of the Examiner, not of those skilled in the art. Had the Examiner appreciated, as a skilled person in the medical art would, ..." Applicant must be assured that all disputes over the meaning and scope of terms are

rooted in genuine concern over the merits, *i.e.* the questions of law and underlying facts. In order to assuage any concerns Applicant may have regarding the expertise of the examiner, Applicant is advised that the current examiner holds a Ph.D. in Cell and Developmental Biology, has taught separate courses in Cell Biology, Developmental Biology, and Immunology at the college level, and is first author of papers dealing with growth factors published in peer-reviewed journals. The Examiner's *c.v.* is offered for entry into the record upon request. Applicant may be assured that this examiner is well acquainted with the terms commonly used in the art to describe cells, growth factors, and related phenomena.

Rejections Maintained

35 U.S.C. § 112, Second Paragraph

6. Rejection of Claims 383, 384, 391, 393, and 394 under 35 U.S.C. § 112, second paragraph, is maintained for reasons of record, and hereby extended to include claims 386 and 392. Applicant's arguments filed 04/30/2007 have been fully considered but are not found to be persuasive for the following reasons.

7. On page 21 of the remarks filed 04/30/2007, Applicant posits that, "the number of types of cells that may be multifactorial and non-specific is not relevant to the understanding and definiteness of these disputed terms". Quite the opposite is true. The number of types of cells that may be multifactorial and non-specific is not merely relevant, it is at the heart of the issue. The terms "multifactorial and non-specific" are presented as limitations that define a subset of the cells recited in independent claim 382. By its recitation in a patent claim, the expression

"multifactorial and non-specific" must be intended to lead the skilled artisan to include certain cells and exclude others. Applicant goes to great length to provide support for the idea that "multifactorial and non-specific" *can be* applied to "cells" (pages 7-26 in the response filed 04/30/2007). The question is not whether these terms *can be* applied to cells. The question is, *when* these terms are applied to cells, does the resultant combination, "cells are multifactorial and non-specific" serve to apprise one of skill in the art of the metes and bounds of a patent claim.

8. As noted in the office action of 02/07/2007, claim 383 purports to further limit the generic "cells" of claim 382, by applying the limitations "multifactorial and non-specific". Claim 384, in turn, supposedly further limits the "multifactorial and non-specific" cells of claim 383, by applying the limitation "stem cells". Claim 391 purports to further limit the generic cells of claim 382, by applying the limitation "pluripotent". Claim 393 purports to further limit the pluripotent cells of claim 391 by applying the limitation "stem cells". Claim 394, purports to further limit the pluripotent stem cells of claim 393, by applying the limitation "multifactorial and non-specific". Therefore, stem cells are a subset of "multifactorial and non-specific cells" in claim 384 and "multifactorial and non-specific" cells are a subset of stem cells in claim 394. Even if the expression "multifactorial and non-specific" had an accepted meaning, this web of claim dependencies would obscure it. The claims set forth mutually exclusive meanings for the breadth of the expression "multifactorial and non-specific", as applied to cells. How then, would a practitioner of the claimed methods, or a potential infringer, be able to use the expression "multifactorial and non-specific" as an indicator of which cells are included or excluded? Therefore, the claims, taken together, are subject to rejection under 35 U.S.C. § 112(2) regardless

of any meaning Applicant wishes to attach to the expression "multifactorial and non-specific". Furthermore, since "multifactorial and non-specific cells" must be either broader or narrower than "stem cells", it follows that either claim 384 or claim 394 should be subject to objection under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the base claims. No objection is being made because, given the lack clarity, the examiner cannot tell which claim to pick for objection. Until this situation is corrected by amendment or cancellation of claims, further argumentation as to the meaning of these claim terms will be fruitless.

9. In the event that Applicant should decide that "multifactorial and non-specific" is either broader or narrower than "stem cell", and amend the claims accordingly, a clear understanding of meaning of these terms will still be required to notify the skilled artisan as to the metes and bounds of the claims. With the expectation of forthcoming amendments, Applicant's arguments regarding the meaning of the expression "multifactorial and non-specific" as applied to cells, filed 04/30/2007 have been fully considered and found to be not persuasive for the following reasons.

10. The dispute can be broadly divided into two related questions: (1) Does the expression "multifactorial and non-specific cells" have a well-known, limiting meaning in the art, or (2) does the instant disclosure provide a clear, limiting definition. An affirmative answer to either of these questions would resolve the dispute and the rejection would be withdrawn.

11. As Applicant has noted repeatedly, the claims of a patent are generally given their ordinary and customary meaning in the art. Applicant provides (page 19) an example of the ordinary and customary meaning of the term "multifactorial" in the form of a definition from Merriam Webster's Medline Plus Medical Dictionary: "(adjective) having, involving, or

produced by a variety of elements or causes". What cells do not involve a variety of elements? All living cells are multifactorial by this definition. Does any cell have a variety of causes? What is a "cause" in relation to cells? This dictionary definition underscores the basis of the rejection because by this definition "multifactorial" does not establish any clear metes and bounds when it is used to describe cells.

12. On page 9, Applicant uses an analogy to the term "catalyst" to argue that,

> "...the terms "multifactorial" and "non-specific" relate to future effects of growth factors, including cellular growth factors. By being capable of achieving a given result through the performance of more than one factor, growth factors are deemed to be multifactorial. Moreover, the ability to achieve more than one specific result renders a growth factor to be non-specific."

This explanation was not given in the specification, but even if it were, it would not clarify the issue. The claims recite the result of "producing and integrating a tissue". This is a complex process. Setting Applicant's dubious conflation of the terms "growth factor" and "cell" aside for the moment, one must ask, what cell that is capable of producing and integrating a tissue, would not do so through the performance of more than one factor? Again this view of the meaning of "multifactorial" fails to provide a basis for including some cells and excluding others.

13. The rejections of record have made the point that the term "multifactorial and nonspecific" simply is not used in the art to describe cells. No evidence has been brought forth to establish otherwise. In addition to evidence of record, an EAST search covering all Patents and published applications in the US, Europe, Japan, all PCT applications and the Derwent worldwide patent database yielded 2772 instances of the word "multifactorial". Of these, none (0) had "multifactorial" adjacent to "cell". Therefore, no inventor has ever directly modified the word "cell" or "cells" (the search automatically includes plurals) with the adjective

"multifactorial". Applicant is the only inventor to use the words "multifactorial", "nonspecific" and "cell" in a single sentence; only two patent documents other than Applicant's contain all three terms in a single paragraph. Of these, US 5616490, separately uses "multifactorial" and "nonspecific" to describe the mechanism of action of corticosteroids (column 2, lines 14-16 and lines 29-30). US 6458767 refers to a multifactorial dysregulation of the immune system and therapeutic strategies focusing on nonspecific, systemic blockage of TGF-.beta (column 17, lines 20-21 and lines 31-32). These examples support the rejection of record, which holds that the term "multifactorial," given its ordinary and customary usage in the art, is used to describe causes, effects and processes, not cells.

14. Applicant's arguments repeatedly rely on the concept of "cell as a specie of growth factor". Page 20 of the instant specification teaches that, "As used herein, the term growth factor encompasses compositions and living organisms which promote the growth of hard tissue, such as bone, or soft tissue in the body of a patient...The living organisms can be bacteria, viruses, or any other living organism which promote tissue growth." The genus of "living organisms" is very large. Taxonomists now recognize over 1 million species of living organism (Catalogue of Life, http://www.catalogueoflife.org/info_about_col.php). It has been established on the record in this case that "cells" are a subgenus within "living organisms". Therefore, *in the lexicon of this specification*, "cells" may be a subgenus of "growth factor". Building on this concept, Applicant relies on a literature searches for the expression "multifactorial growth factor" to justify use of the expression "multifactorial cell". This argument is not persuasive because the concept of "cell as a specie of growth factor" does not exist in the art. First, consider the following dictionary definitions of "growth factors":

From the Online Medical Dictionary:

> **growth factors**
>
> Proteins involved in cell differentiation and growth. Growth factors are essential to the normal cell cycle, and are thus vital elements in the life of animals from conception to death. Among other things, they mediate foetal development, play a role in maintenance and repair of tissues, stimulate production of blood cells, and, gone awry, participate in cancerous processes.

From the Dictionary of Cancer Terms:

> growth factor
>
> A substance made by the body that functions to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy.

From the Life Science Dictionary:

> 2. **growth factor**
> **Author:** Susan A.Hagedorn
> **Definition:** A serum protein that stimulates cell division when it binds to its cell-surface receptor.

Alberts *et al.*, in Molecular Biology of the Cell, 4th Ed, 2002, write in Chapter 17:

> The factors that promote organ or organism growth can be operationally divided into three major classes:
>
> 1. *Mitogens,* which stimulate cell division, primarily by relieving intracellular negative controls that otherwise block progress through the cell cycle.
>
> 2. *Growth factors,* which stimulate cell growth (an increase in cell mass) by promoting the synthesis of proteins and other macromolecules and by inhibiting their degradation.
>
> 3. *Survival factors,* which promote cell survival by suppressing apoptosis.
> Some extracellular signal molecules promote all of these processes, while others promote one or two of them. Indeed, the term *growth factor* is often used

> inappropriately to describe a factor that has any of these activities. Even worse, the term *cell growth* is often used to mean an increase in cell number, or *cell proliferation.*

Although Alberts *et al.*, call for a precise definition that is slightly at odds with the dictionary definitions cited above, all sources agree that a "growth factor" is "a factor that acts upon cells" not "a factor which *is* a cell", as Applicant wishes for it to mean. Therefore, expressions such as "growth factors, including cells, such as stem cells" or "cellular growth factors such as stem cells" are outside of the ordinary usage of these terms, regardless of the academic degree held by the person using them.

15. An EAST search covering the worldwide patent literature yielded 367 documents wherein the expression "cellular growth factor" as not part of the expression "cellular growth factor receptors". This criterion was chosen because the expression "cellular growth factor receptors", of course, refers to receptor molecules on cells. The "key word in context" results for all 367 documents will be entered into the record as Examiner's search notes. The results will, therefore, be available to Applicant through PAIR. In all 367 documents the Examiner found not a single instance where "cellular growth factor" could be logically construed to mean "a growth factor which is a cell" as Applicant wishes for it to mean. In the few instances where the key word in context leaves room for doubt, the associated full specification always confirms that the term "cellular growth factor" always means "a factor that acts upon cells". With regard to non-patent literature, a search of Medical Subject Headings database maintained by the National Library of Medicine (http://www.nlm.nih.gov/mesh/2007/MBrowser.html), using "growth factor" as the query term, yields a 24-page list of factors (see search notes). Not one cell is listed.

16. Therefore, in view of the foregoing medical dictionary definitions, textbook definition, and literature searches, Applicant's use of the term "cellular growth factor" to mean "a growth factor which is a cell" is inconsistent with the ordinary meaning of the term whenever it appears outside of the instant specification. It follows that references in the literature to multifactorial or nonspecific *growth factors* have no relevance to the meaning of "multifactorial and nonspecific" as applied to *cells*.

17. On page 23, cites Caplan 2001 as teaching that bone marrow stem cells undergo a multifactorial differentiation pathway. Contrary to Applicant's assertion, this usage of the term "multifactorial" is not consistent with Applicant's use of the term. Clearly, the adjective "multifactorial" does not modify "cells", it modifies "pathway". Applicant argues (p.23) that Caplan 1991 clearly characterizes mesenchymal stem cells as multifactorial cells because more than one factor is described. The quoted passage from Caplan 1991 begins, "Their progeny are affected by a number of factors..." While this passage does describe mesenchymal stem cells as being affected by multiple factors, it does not use the term "multifactorial cell" nor does it provide guidance for the boundary of the set of multifactorial cells. Neither Caplan reference teaches that certain cells are multifactorial and others are not. Therefore, even if Caplan 1991 and 2001 were interpreted as teaching that mesenchymal stem cells are multifactorial, they would only support that application of "multifactorial" to mesenchymal stem cells. None of the instant claims are limited to, or even recite, mesenchymal stem cells. This is for good reason, because the instant specification does not mention mesenchymal stem cells. Therefore, the Caplan references do not provide support for the use of "multifactorial" as a limitation of "cells" in the instant claims.

18. With regard to the term "nonspecific" as applied to cells, Applicant, cites Caplan 1991 as disclosing that MSC are lineage-nonspecific. From this, Applicant concludes that, "it is patently clear that a person skilled in the art understands the meaning of the term "non-specific" when applied to cells, such as stem cells - they are lineage-nonspecific and can develop into a variety of tissues." Note, however, that Caplan carefully connected "lineage" to "nonspecific" to make it perfectly clear what kind of specificity was being addressed. The instant application does not mention *lineage* specificity or non-specificity—if the expression "lineage non-specific" had been used, a step toward clarity would have been taken. Furthermore, in claim 383, "non-specific" is not used to describe only stem cells; it applies to the "cells" of claim 382. "Non-specific" can have many meanings when applied to "cells". Steinman (Proc Natl Acad Sci U S A. 1996 Mar 19; 93(6):2253-2256) uses the term "nonspecific cells" to describe T cells with no specificity for autoantigens (see Abstract). In US Patent Application Publication 20050124043, the term "nonspecific cells" is used to denote cells that bind nonspecifically to a test membrane [0161], likewise US 20040048260 at [0015]. In US 5258453, at column 50, lines 1-2, a nonspecific cell line is one without secretin receptors.

19. The search for a limiting definition for "multifactorial and nonspecific" as applied to cells therefore turns to the instant disclosure. Applicant (p.9) has directed the Examiner's attention to page 37, lines 19-22, where cells, such as stem cells and germinal cells, are described to be "multifactorial and nonspecific." An exemplary list is not a definition. If this is taken to be a definition, then on what basis does Applicant claim "multifactorial and nonspecific" cells to be subset of stem cells in claim 394? Applicant has specifically argued (p.15) that not all stem cells are multifactorial and nonspecific, and not all multifactorial and nonspecific cells are stem cells.

Thus, Applicant points to the very reason that the claims are being rejected under 35 U.S.C. § 112, second paragraph: What cells are included or excluded by the limitation "multifactorial and nonspecific"? Furthermore, page 37, lines 19-22 of the specification, attempts to provide a functional definition for "multifactorial and nonspecific" cells by stating that they "can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated." The rejection of record appropriately points out that this functional portion of the definition makes no sense. Applicant's arguments and evidence on this issue have been addressed in the record. The terms "angiogenic cascade" and "genetic cascade" are NOT the same as the term "cascade of genetic *material*." Applicant (p. 18) now asks, "Is the Examiner maintaining that the terminology used in the above two publications makes sense, but the nearly identical terminology cited by Applicant does not?" The answer is, yes.

20. First, consider the ordinary meaning of the term "cascade" as used in biology and medicine:

The Life Science Dictionary:

1. **cascade**
Definition:
An entire series of reactions which occurs as a result of a single trigger reaction or compound.

Dorland's Illustrated Medical Dictionary:

cascade (cas·cade) (kas-kād′) a series of steps or stages (as of a physiological process) that once initiated continues to the final step by virtue of each step being triggered by the preceding one, sometimes with cumulative effect.

coagulation c. the series of steps beginning with activation of the intrinsic or extrinsic pathways of coagulation, or of one of the related alternative pathways, and proceeding through the common pathway of

> coagulation to the formation of the fibrin clot; each step involves zymogen activation, the activated zymogen catalyzing activation of the following step.

21. Therefore, in biology or medicine, a "cascade" is "series of reactions" or a "series of steps, each step being triggered by the preceding one". The coagulation cascade is, for example, a series of reactions, or steps, involving proteins. It would be inaccurate or incomplete to call it "a cascade of proteins". Likewise, the expression "angiogenic cascade", as used in the Augustin reference of record, evokes an image of a series of steps or stages. Augustin refers to VEGF as acting at an early point in a hierarchical order of morphogenic *events* (page 645, left column; emphasis added). The "genetic cascade" referred to by Dr. Bahary (of record) logically indicates a series of genetic steps or events, such as sequential activation of genes. Dr. Bahary alludes to this by describing his effort to "analyze their temporal-spatial expression", referring to genes. "Material" does not mean "reactions", "steps", "events", or "temporal-spatial expression". In contrast to "genetic cascade", the expression "cascade of genetic material" evokes an image of a DNA preparation being spilled from the laboratory bench.

22. Even if the malapropism of "cascade of genetic material" is ignored and the expression is taken to be equivalent to "genetic cascade", this generic function does not help in determining the metes and bounds of "multifactorial" and nonspecific cells". Which gene activation events are and are not activated by "multifactorial" and nonspecific cells"?

23. Finally, Applicant argues "multifactorial" and nonspecific cells" is definite because Drs. Heuser and Lorincz read and understood such terminology. Various kinds of cells are mentioned for various uses in the specification. The experts may have grasped that Applicant intended that

certain types of cells were to be used, but they do not say that reading the words "multifactorial and non-specific" guided them as to which cells to use.

24. To reiterate, with respect to 35 U.S.C. § 112, second paragraph, the question is not whether "multifactorial and non-specific"*can be* applied to cells. The question is, *when* these terms are applied to cells, does the resultant combination, "cells are multifactorial and non-specific" serve to apprise one of skill in the art of the metes and bounds of a patent claim. Even after considering Applicant's arguments, it is still not clear how "multifactorial and non-specific" fulfils the purpose of apprising the skilled artisan as to which cells are to be used and which cells are not.

25. The rejection of record extends to Claims 386 and 392 because these claims depend from rejected claims 383 and 391, respectively. The limitations in claims 386 and 392 do not correct the lack of clarity in the base claims and, therefore, these claims properly should have been included in the rejection of record.

26. Rejection of Claim 404 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. Applicant's arguments filed 04/30/2007 have been fully considered but they are not persuasive. The rejection of record holds that claim 404 introduces new matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection finds no support

for the limitation of administration of cells to a damaged site in a leg of a patient in the specification as originally filed.

27. Two aspects of description are lacking. First is the location of sites of the desired soft tissue and administration of cells. Example 18 of the specification discloses administration of DNA to a damaged artery in a leg. Claim 404 recites a broader scope of a damaged *site* in a leg. In response, Applicant argues (p.27-28) that, "the specification as filed is replete with disclosure relating to the concept of administering growth factors to a "desired site" in the body for promoting the growth of soft tissue, such as an artery, as exemplified on page 45 and in Example 18 of the specification." New or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement. See, e.g., In re Lukach, 442 F.2d 967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range). Here "in the body" is a genus, "a damaged site in a leg " is a subgenus range, and the artery of Example 18 is a specific example within the subgenus range. See also, In re Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads). A further matter not previously stated, is the fact that Example 18 specifically teaches administration to arterial walls (page 53, lines 20-28) and, therefore, does not support the recitation of intramuscular injection in claim 404.

28. The second aspect wherein description is lacking is with respect to the agent to be administered. Example 18 prophetically teaches administration of plasmid DNA and does not envision administration of *cells* at the damaged artery. In response, Applicant argues (p.28) that "appropriate growth factors within the scope of Applicant's invention are described as

comprising living organisms (page 20), such as cells (page 37), or a patient's own cells (pages 47 and 48) and particularly stem cells (pages 37, 40, 41, 42, 46, 48, 51 etc.) such as bone marrow stem cells (bone marrow mononuclear cells/BMCs) and germinal cells." It is agreed that the specification postulates that cells may be used for a variety of purposes. The claim in question, however, specifically recites a subgenus of cells, stem cells, for the purpose of growing a specific type of organ, an artery, at a specific site, a damaged site in a leg of a patient. The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

29. Page 20 of the specification teaches that, "As used herein, the term growth factor encompasses compositions and living organisms which promote the growth of hard tissue, such as bone, or soft tissue in the body of a patient...The living organisms can be bacteria, viruses, or any other living organism which promote tissue growth." The genus of "living organisms" is very large. Taxonomists now recognize over 1 million species of living organism (Catalogue of Life, http://www.catalogueoflife.org/info_about_col.php). It has been established on the record in this case that "cells" are a subgenus within "living organisms". Therefore, *in the lexicon of this specification*, cells may be a subgenus of growth factor. Applicant then asserts that Claim 404 is directed to an alternative embodiment to the growth factor of Example 18. It has been established in elsewhere in this office action that the art outside of the instant specification

provides no support at all for the concept of "cell as a specie of growth factor". Even the instant application never clearly enunciates the concept of "cell as a specie of growth factor". Instead, Applicant relies of the teaching that living organisms can be growth factors (specification p. 20), the fact that cells are organisms, and separate teachings in the specification that suggest that cells may do some of the same things that growth factors do. Even within the lexicon of the instant specification, it should be clear that "cells" and "VEGF cDNA" are so structurally and functionally distinct that they must belong to distinct subgenera within "growth factors". Again, new or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement. See, e.g., In re Lukach, 442 F.2d 967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range). Here, Applicant relies on one specific example within the genus of growth factors (VEGF cDNA) to support a subgenus that is clearly distinct in its structure and mode of action. There simply is no rational scientific basis for one of skill in the art to read "VEGF cDNA" and think "stem cell", without being specifically prompted to do so. The instant specification does not provide that prompting.

30. Therefore, the specification as filed does not reasonably lead the skilled artisan to either the agent to be administered or the site of administration, and therefore the introduction of this combination of limitations in claim 404 in the amendment filed 11/03/2006 constitutes new matter.

31. Rejection of Claims 382-405 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained and hereby extended to include new claim 406. Applicant's arguments filed 04/30/2007 have been fully considered but they are not persuasive.

32. A first aspect of the rejection of record concerns the breadth of the claims. Claim 382 recites placing cells into the body of a patient. Applicant repeatedly argues that the specification teaches the use of stem cells and germinal cells, but the claim is not so limited. It does not matter that processing bone marrow and peripheral blood for recovering mononuclear stem cells was routine in the medical art prior to Applicant's invention (hereby acknowledged as per Applicant's request on page 40). The claim defines the invention. The cell of claim 382 could be any of the more than 200 cell types of the human body, or any bacterial cell or any cell from any of the more than 1 million species of living organism. The extent to which any of the dependent claims narrow the genus of cells to be administered is uncertain, for reasons detailed in the rejections under 35 USC 112(2). Any of these cells are recited for use in forming any soft tissue at any site in a human. In claim 385, "cells" are recited to form any soft tissue *plus a new artery* at any site. As previously noted, the specification broadly asserts that the administration of cells can achieve diverse effects, including growth of any "hard" tissue or "soft" tissue (p. 20), formation of entire new organs (p. 32) or portions of organs (p. 46), restoration of function in any organ (p. 47), formation of auxiliary organs (p. 49), correction of necrosis (p. 49), replacement of missing limbs or body parts (p. 50), treatment of inflammation (p. 50), correction of musculoskeletal injuries or deficiencies (p. 50), formation of hybrid organs (p. 50), etc. No guidance or details are provided as to *how* to achieve these remarkable effects, most of which have never been achieved in this art to this day. The lack of detail in the specification, in contrast to the actual

amount of experimentation required to accomplish similar techniques has been noted in the record. Applicant's assertion that Stauer (of record) did not need much experimentation to use bone marrow stem cells to successfully treat MI (paragraph bridging pages 33-34) misses the point: Stauer used one kind of stem cell to achieve one outcome. Applicant's argument also unduly dismisses the difference between performing work, actually achieving as result, and providing guidance as to how one of skill in the art may reproduce the result (as done by Stauer), and simply making an assertion that a result will occur (as provided by the instant specification).

33. With respect to a specific organ, an artery, recited in the instant claims, Example 18 (pages 53-55), together with the following excerpts from the specification include all of the specific teaching about the growth of arteries:

> Page 44, llines 22-24: For example, the vascular epithelial growth factor gene (VEGF) or its growth factor equivalent can be inserted into the body to cause an artery to grow.

> Page 45, lines 1-16: An artery can be grown in the heart, legs, or other areas by injecting a gene or other genetic material into muscle at a desired site. Size, vascularity, simplicity of access, ease of exploitation, and any other desired factors can be utilized in selecting a desired site. The gene is one of several known VEGF genes which cause the production of vascular endothelial growth factors. Several VEGF genes which produce vascular endothelial growth factors are believed to exist because nature intends for there to be several pathways (i.e., genes) which enable the production of necessary growth factors. The existence of several pathways is believed important because if one of the genes is damaged or inoperative, other similar genes can still orchestrate the production of necessary growth factors. VEGF genes are used by the body to promote blood vessel growth. VEGF genes are assimilated (taken in) by muscle cells. The genes cause the muscle cells to make a VEGF protein which promotes the growth of new arteries. VEGF proteins can be made in a lab and injected into a patient intravenously, intraluminally, or intramuscularly to promote the growth of an artery. Or, the genes (or other genetic material) can be applied with an angioplasty balloon, with the assistance of a vector, or by any other method.

> Page 45, lines 19-21: An injection of a gene to form cardiac muscle and/or an injection of a gene to form an artery can be utilized to revive or replace the dead portion of the heart.

> Page 52, lines 17-19: Gene products can be inserted in a patient's body to produce an organ or other structure. For example, VEGF growth factor inserted in the body produces an organ, i.e., an artery.

34. Clearly, no mention is made of attempting to grow an artery by placing cells in the body. These passages do not even evoke Applicant's dubious inclusion of "cell" within the definition of "growth factor". In order to construe these passages as teaching the use of stem cells, one would have to construe the term "genetic material" as directing the skilled artisan to stem cells. Such an interpretation would be at odds with the normal usage of these terms in the art and inconsistent with the way the terms "genetic material" and "stem cell" are used in the instant specification.

35. Example 18 of the instant specification provides a prophetic example in which VEGF cDNA is introduced into a patient to induce angiogenesis. The rejection of record is based, in part, on the fact that the example does not provide guidance or even suggest the use of cells. In response, Applicant generally argues that VEGF cDNA is a growth factor and that whenever the specification uses the term "growth factor" the reader should think "cells". It has been pointed out elsewhere that, although the lexicon of this specification permits inclusion of "cells" within the genus of "growth factors", the specification does not lead the skilled artisan to the particular subgenus of "cells" whenever growth factors are mentioned. Applicant further argues (p. 39) that "the Examiner has failed to establish why one skilled in the art would not be able to extrapolate those examples across the entire scope of the claims include the use of cells, *i.e.* stem cells as the growth factor". Apparently in expectation that the instant office action would include the explanation that was allegedly lacking in the previous actions, Applicant has submitted, on

05/25/2007, declarations by Drs. Lorincz and Heuser, which had been in response to a rejection in copending application 10/179589. Thus, in effect, Applicant has supplied a rebuttal to an argument that has yet to be made in this case. Applicant now argues that the skilled artisan would be guided in the use of cells by converting the amount of plasmid DNA in the example to cellular equivalents. The facts in the instant case are similar to those in copending application 10/179589, the difference being that the proposed method of converting plasmid DNA to cell equivalents was introduced into 10/179589 as part of Applicant's remarks made in response to a rejection whereas the same method first appears in this case as Exhibits D of the Lorincz and Heuser declarations. The following excerpt from the office action mailed on 03/07/2007 in copending application 10/179589 is provided in order to present the argument that prompted the Lorincz and Heuser declarations, and thereby clarify and complete the record in the instant case.

> Applicant admits on page 9 that Examples 17-19 employ nucleic acids, but asserts that one skilled in the art reading the specification, which teaches that cells, i.e., stem cells (BMC's) possess equivalent activity to genes (nucleic acids) and other genetic material in forming a new artery (i.e., promote morphogenesis of an organ—artery), would be able to easily extrapolate the number on a weight basis of mononuclear cells required to obtain equivalent results. According to the method for extrapolation provided in the footnote to pages 10-11, 250 μg of plasmid DNA (an amount described in Examples 17 and 18) divided by 40 pg, (asserted to be is the average DNA content of a cell; the species of cell is not disclosed) equals 6.25×10^6, and therefore the Examples 17 and 18 instruct the skilled artisan to use 6.25×10^6 cells. This argument is not persuasive for several reasons. First, this method of converting plasmid DNA to cell equivalents is not included in the specification as filed. This is important because one of skill in the art would never think to attempt such an extrapolation. The unsound scientific basis for the conversion of μg of plasmid DNA to cellular equivalents would be obvious to anyone trained in molecular biology. One basic assumption of the recited conversion is that the 40 pg of cellular DNA comprises the same gene dosage a purified plasmid DNA. Every molecule of the postulated plasmid DNA comprises a copy of the VEGF cDNA. In contrast, VEGF coding sequences would comprise but one of 30-40 thousand genes in genomic DNA (at the time of filing, it was widely believed that the human genome comprised 100,000 genes). Therefore, one of skill in the art at the time of filing would not expect plasmid DNA and genomic DNA to be comparable on a per weight basis. Applicant's argument seems to view the living cell as little more than a container for DNA. The expression of

the recombinant cDNA would be under control of the limited number of enhancer and promoter elements in the plasmid, as opposed the native control elements with the genome. Therefore, even equivalent gene doses would not be expected to yield equivalent amounts of gene product with a plasmid as opposed to a cell. Applicant's argument seems to view the living cell as little more than a container for DNA. Delivery of the genes to a target as recombinant DNA as opposed to native genes within a living cell are technically different processes; there is no basis for using one to guide the other. For example, with DNA one is concerned with chemical stability, efficiency of uptake, stable retention, and subsequent expression of the injected molecule into target cells, whereas with cells separate issues of formation of effective attachment to ECM and neighboring cells, short- and long-term viability, and responses to environmental cues arise. As evidence, one need look no further than the US Patent classification system. Methods of *in vivo* treatments involving whole live cells as opposed to nucleic acids are separately classified: class 424 subclass 93.1 (cells); class 514, subclass 44 (polynucleotides). These separate classifications indicate a different status in the art such that it is well known that cell therapy and gene therapy are not obvious variants of one another.

36. The Examiner hereby expressly applies the foregoing argument in support of the rejection of instant claims 382-406 under 35 USC 112, first paragraph, as lacking enablement. The question at hand is whether example 18 provides guidance to one of skill in the art to use cells in place of the VEGF cDNA in the example. Within this larger question, there is the specific question of whether it is scientifically sound to use the amount of plasmid DNA in the example to extrapolate a number of cells to use, and whether one of skill in the art would be prompted to attempt such a conversion without being specifically told to do so. No such extrapolation is taught the instant specification. A specific method for making this extrapolation was first entered the record in this case only as Exhibits D of the Lorincz and Heuser declarations filed on 05/25/2007. Therefore, this extrapolation is only under discussion because Applicant apparently seeks to establish that an extrapolation of this type is so well known in the art that it would be implicitly understood to be present in example 18 of the specification. The rejection now of

record states that one of skill in the art would never think to attempt such an extrapolation because its scientific basis is unsound.

37. Clearly, the person of skill in the art would be familiar with the construction and manipulation of plasmids, and the techniques wherein plasmid vectors are introduced into cells to bring about the expression of genes. Thus, in this matter, the art is unquestionably molecular biology. While it is acknowledged that the fields that may be described as "medical arts" and "molecular biology" overlap considerably, expertise in "medical arts" does not make one an expert in molecular biology any more than expertise in any one medical specialty makes one an expert in any other medical specialty.

38. Since the independent declarations of Drs. Lorincz and Heuser are identical *verbatim*, they will be responded to jointly. Drs. Lorincz and Heuser state that studies involving conversion of the average content of nucleic acids per cell in human marrow cell have been routinely conducted and accepted by skilled scientists for over 50 years. Drs. Lorincz and Heuser supplied excerpts from three publications illustrating such conversion. Drs. Lorincz and Heuser further state that DNA content is substantially consistent from tissues of any given species. None of these facts are disputed. None of these facts speak to the issue at hand. Example 18 describes the administration of a *plasmid DNA vector comprising VEGF cDNA*. The conversion under discussion purports to calculate a number of cells based an amount of *plasmid* DNA. The term plasmid was coined in 1952 (Plasmids; Histories of a Concept, http://histmicro.yale.edu/mainfram.htm). Techniques for making cDNA (copy DNA made by reverse transcription of mRNA), and for using plasmid vectors propagate and express cDNA in cells were developed in the 1970s. Scientists 50 years prior to the filing date of the instant

application (1998) would not recognize the terminology or even imagine the concept of the conversion depicted in Exhibit D. Yet, Drs. Lorincz and Heuser conclude that the conversion depicted in Exhibit D is consistent with the extrapolations that have been performed for over 50 years. This carefully worded conclusion is not challenged, but it is clear that the consistency extends only to the point that the extrapolations involve math and DNA; any further comparisons would be impossible.

39. Isner et al., (*Circulation.* 1995;91:2687-2692) describe construction of the plasmid phVEGF$_{165}$, which appears to be the model for the plasmids mentioned in the specification. According to Isner *et al.* phVEGF$_{165}$ consists of a total of 5651 bp (base pairs). Of these, 3,162 bp are from pUC118, 763 bp are the CMV promoter/enhancer, and 1726 bp are VEGF cDNA. Therefore, the plasmid has one copy of VEGF coding sequences per approximately 5.7 kb. According to the data supplied by Drs. Lorincz and Heuser, in the table labeled "II. Some useful nucleotide dimensions", humans have 3 x 10^9 base pairs per haploid genome. This converts to 3 x 10^6 kb. Assuming 1 VEGF gene per haploid genome, 3 x 10^6 kb of human genomic DNA contains the same number of VEGF genes as 5.7 kb of the plasmid phVEGF$_{165}$. Therefore, the amount of VEGF coding sequence in an equal mass of human genomic DNA and VEGF plasmid DNA differs by a factor of 5.26 x10^5. Inclusion of placental growth factor (PlGF), VEGF-B, -C, and –D as "VEGF genes" would reduce this factor to about 1 x 10^5. Therefore, it is fundamentally illogical to equate recombinant plasmid DNA to cellular DNA.

40. Of course, one of skill in the art of molecular biology would understand that the concept of the foregoing paragraph was embodied in the sentences, "Every molecule of the postulated plasmid DNA comprises a copy of the VEGF cDNA. In contrast, VEGF coding sequences would

comprise but one of 30-40 thousand genes in genomic DNA (at the time of filing, it was widely believed that the human genome comprised 100,000 genes). Therefore, one of skill in the art at the time of filing would not expect plasmid DNA and genomic DNA to be comparable on a per weight basis." Drs. Lorincz and Heuser "read and understood" these sentences but did not comment on them. While it is tempting to speculate that the Declarant's silence could be attributed to the fact that molecular biology is not their specialty, it rather seems more likely that Drs. Lorincz and Heuser were carefully refraining from attempting to refute an argument they know to be correct.

41. Neither the Declarants nor Applicant have responded to the criticism that the above referenced method of extrapolating plasmid DNA to cell number seems to view the living cell as little more than a container for DNA. When DNA in a blood sample is used to calculate the number of cells in the sample (as in the methods cited by the Declarants), the goal is simply to calculate a number of cells. However, the person of skill in the art would want to know a number of cells required *to achieve the same result as the plasmid DNA* in Example 18. One of skill in the art would not expect to be able to predict this simply extrapolating DNA content. Delivery of the genes to a target as recombinant DNA as opposed to native genes within a living cell are technically different processes for many reasons, as noted in the excerpt from the office action mailed on 03/07/2007 in copending application 10/179589 quoted above. Unlike $phVEGF_{165}$, a cell is not a single molecule designed for expression of a single gene.

42. Therefore, for at least the reasons cited above, Example 18 does even implicitly guide or even suggest any method wherein cells are administered to grow an artery or any other organ.

43. Another aspect of the rejection of record concerns step (b) of the independent claims, which recites forming a bud at said select site in the body of said patient. Applicant argues (pp. 36-37) that one of skill in the art would understand that a bud is a primordium for the formation of soft tissue. Here, Applicant is persuasive to the extent that the term "bud" is sometimes used in developmental biology to denote an *organ* primordium (*e.g.* limb bud). Furthermore, Applicant has supplied a reference, albeit one clearly directed to a non-technical audience, wherein an artery primordium is called a bud (Whitely Clinic website, of record). If, however, all organ primordia are buds, then it would seem that bud formation is intrinsic to all instances of organogenesis. If, by reciting a specific step of bud formation, Applicant means that the practitioner of the method must do something other than place cells in the body, then this limitation is not enabled by the specification. If, by step (c), which recites growing desired tissue...from said bud, Applicant means that the practitioner of the method must recognize that a bud has formed and perform an active process to make it grow, then this limitation is not enabled by the specification. There is no guidance in the specification or in the art specifically for bud formation, or specifically for nurturing buds, for all organs and all of the cells encompassed by the claims. It is further noted that most of the claims are drawn to methods of producing and integrating *tissue*, not organs. Therefore, Applicant's recitation of bud formation makes the method more difficult because it requires that the tissue at least begin to organize into an organ. Bud formation would not be a logical step in a situation where only a single layer of tissue is to be replaced, for example.

44. It is interesting that Applicant has pointed out the Examiner's failure to reject the claims on prior art (p.37). This bears further scrutiny, as it relates to enablement. It is not the case, as

Applicant alleges on page 38, that, "Applicant is the first to teach injecting growth factors... in the body of a human patient to grow in vivo soft tissue, such as an artery." The use of growth factors to stimulate vascularization of the heart has been known at least since the issuance of US 4296100 in 1981, which teaches the use of FGF to treat myocardial infarction. US 4296100 indicates that the effect of FGF is increase vascularization (column 1, lines 23-30), which would include artery formation. Isner et al., (*Circulation.* 1995;91:2687-2692) describe construction of the plasmid phVEGF$_{165}$, which appears to be the model for the plasmids taught in Example 18 in the instant specification. Isner et al., teach, throughout, a protocol wherein phVEGF$_{165}$, is administered to human patients for the purpose of treating peripheral artery disease. The teachings of Isner et al., differ from the methods of the instant claims only teaching administration of a cDNA encoding protein growth factor whereas the instant claims recite administration of cells. According to Applicant's arguments, this difference is so small as to be inconsequential. Applicant argues, for example on p. 41, that, "One reasonably skilled in the art appraised of such knowledge when viewing applicant's specification disclosure would readily be able to predict and comprehend that stem cell growth factors are equivalent to cDNA clones described in Example 18 for providing the desired artery formation." Another example is provided by Applicant's chosen experts, Drs. Lorincz and Heuser, who each state in declarations filed 04/30/2007,

> "Based upon above Paragraphs 3-5, it is my opinion that introducing a growth factor, including cells, and more specifically, stem cells, in the body of a human patient will predictably result in the growth of soft tissue, such as an artery, which will integrate itself into pre-existing tissue of the body thereby forming a unified whole.
>
> Based upon above Paragraphs 3-5, it is my opinion that one skilled in the medical arts, armed with the knowledge in such paragraphs, would be able

to practice the method set forth in Exhibit C without need for resorting to undue experimentation."

45. However, "when viewing applicant's specification" one sees that that the instant specification adds no new technical advance beyond that which is taught in Isner et al. All details about VEGF cDNA (the few that are given) in the instant specification are taught by Isner et al. or references cited therein. Thus, the "prophetic" example relevant to artery formation adds nothing to new to that which was known and published three years before the instant application was filed. In particular, the instant specification does not even begin to work out the procedural differences between the protocol taught by Isner et al, and any method that uses cells instead of cDNA. The instant specification does not show a single organ, part of an organ, tissue, artery, or even a bud formed by placing cells in a body. Applicant generally argues that any teaching in the art or in the instant specification that refers to "growth factors" can be predictably applied to "cells" without experimentation. Applicant argues (p.35) that actual working examples are not a requisite for satisfying the enabling requirement of the statute and prophetic examples are specifically sanctioned by the PTO. Applicant claims to have achieved something no one else had done, and then claims to have achieved it simply by writing it down. Applicant insinuates that that "no more than *common sense* would be required" for Strauer (2005, of record) to successfully treat MI with bone marrow stem cells. By this reasoning, the difference between the instantly claimed methods and those of Isner *et al.* is obvious and a rejection under 35 U.S.C. 103(a) should have been made. (See *KSR v Teleflex* 82 USPQ2d 1385 (U.S. 2007) with regard to "common sense" and obviousness).

46. Whether prophetic examples are sufficient is determined on a case-by-case basis and depends, among other things, upon the nature and complexity of the invention. Applicant (p.41) claims to have "used old and routine administration techniques and old materials to achieve a *remarkable new result*: the growth of soft tissue, i.e. an artery, in the body of a human patient" (emphasis added). It is a remarkable achievement to grow a new artery by implanting cells, *but Applicant did not do it*. It would be even more remarkable to grow any type of organ or tissue at will, which is the scope of claims 382-384, 386, 389, 391, 393-399, and 402. This is why no obviousness rejection is being made. Starting with knowledge that a purified growth factor or a cDNA that encodes a growth factor can stimulate artery formation (*i.e.* the prior art knowledge in US 4296100 and Isner et al.), it is not obvious for one to achieve the same result using a stem cell or any other kind of cell. It is certainly not obvious how to grow any and all organs. To say that growth of an artery using stem cells was obvious in view of prior art in 1998 would be to show extreme disregard of the work performed by Stauer, for example, who actually achieved this result in 2005. Likewise, to say that these non-obvious and remarkable results can be achieved without doing a single experiment is incredible. For at least these reasons, rejection of claims 382-406 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, must be maintained.

New Rejections

Claim Rejections - 35 USC § 112

47. Claims 382-402 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claim 382 recites steps (a) Placing cells *in said body* of said human patient; and (b) Forming a bud *at said selected site* in said body of said human patient. and (c) Growing said desired soft tissue which integrates itself into said body of said human patient *from said bud*. The added emphasis is meant to point out that a literal interpretation of the claim does not require that either the bud of step (b) or the tissue of step (c) have anything to do with the cells of step (a). That is, steps (a) and (b) recite two apparently unrelated actions: placing cells somewhere in the body and forming a bud in the selected site of the preamble. This could be clarified using claim 403 as a model, by adding *at said selected site* to step (a).

48. Claims 382-406 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Step (b) of the independent claims recites forming a bud. It is not clear whether this step refers to an intrinsic step of artery formation that does not require action on the part of the practitioner of the method or as requiring action on the part of the practitioner of the method to form a bud. Clarity on this matter is significant to the enablement of the methods, as noted. Clarity is also critical in determining the scope of the claims, as will be evident in the following prior art rejection and provisional double patenting rejections.

Claim Rejections - 35 USC § 102

49. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

50. Claim 382 is rejected under 35 U.S.C. 102(b) as being anticipated by Sutherland *et al.*, Diabetes. 1980;29 Suppl 1:31-44. Sutherland *et al.* disclose autotransplantation of dispersed pancreatic islet tissue (which necessarily comprises cells) into the portal vein in three patients who underwent near-total (greater than 97%) pancreatectomy (see Abstract). Thus, Sutherland *et al.* performed the only active step recited in instant claim 382, *i.e.* placing cells in the body of human patient. In Sutherland *et al.*, engraftment was indicated by the lack of a requirement for exongenous insulin; "integration" was shown histologically by the presence of islets (a desired soft tissue) in the liver parenchyma.

Double Patenting

51. Claim 388 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 159 of copending Application No. 10179589. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. The two claims recite identical methods of producing and integrating an artery at a selected site in a body of a

human patient comprising placing a cell in a body of a human patient and growing said desired artery. Step (b) of instant claim 388 (from claim 382) is interpreted as reciting an intrinsic step of artery formation that does not require action on the part of the practitioner of the method.

52. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

53. Claim 388 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 159 of copending Application No. 10179589. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 388 is a species of the generic method of claim 159. Here, step (b) of instant claim 388 (from claim 382) is interpreted as requiring action on the part of the practitioner of the method to form a bud.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

54. Claims 382-406 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 159, 163, and 170-173 of copending Application No. 10179589. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The following relationships are noted with the proviso that an exact determination of the obviousness and genus-species relationships among the respective claims is obscured by the possibility of alternative interpretations of step (b) in independent claims 382 and 403 as noted above. Claims 159, 163, and 170-173 of copending Application No. 10179589 are drawn to methods of growing and integrating a desired artery comprising steps of placing a cell in a body of a human patient. This method differs from that of instant claim 403 only by the recitation of "stem cells" in claim 403 as compared to the generic "cells" of claim 159. This difference is rendered obvious by the recitations of stem cells in copending claims 163 and 170. Furthermore, "growing and integrating a desired artery" (copending claim 159) is a species of the generic "producing and integrating tissue" of instant claims 382-384, 386, 389, 391, 393-399, and 402. This difference is rendered obvious by recitation of an artery in instant claims 385, 400, and 406. The respective dependent claims recite further limitations regarding sites of injection and observing results, which are identical, obvious variants, or are related as genus-species.

Conclusion

55. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD whose telephone number is 571 272 . 1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571 272 0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DAVID ROMEO/
PRIMARY EXAMINER
ART UNIT 1647

DCG
Art Unit 1647
20 July 2007